REMARKS

I. Objections to the Specification

The Examiner objected to claims 35-36 and 38 as being in improper dependent form. The claims have been amended to clarify the dependency.

The Examiner maintains the objection to Applicants' priority claim. As evidenced by the discussion of the cited documents below, the priority claim is not necessary to overcome the disclosure of the documents so further discussion of the merits of the priority claims is not required. Applicants will address the issue in other applications if it is ever necessary.

II. New Grounds of Objection/Rejection and Amendment to the Specification

The Examiner raises a new ground for rejection, indicating that trademarks in the application are improperly designated.

The Examiner also indicates that the word "protein" is misspelled at page 51 of the specification.

In response, the specification has been amended to properly designate trademarks used in the application and also to correct the misspelling noted by the Examiner.

The amendment does not introduce new matter.

III. Support for Amendments to the Claims

The amendment to claim 23 amends the phrase "when the hinge peptide contains two cysteines the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally occurring IgG or IgA antibody is not deleted or substituted" the Examiner interpreted as conditional. The amendment to claim 24 finds support at page 12, lines 10-12. The amendments to claims 35-36 and 38 were made to correct claim dependencies. Support for new claims 146-148 can be found in claims 35-36 and 38.

The amendments to the claims do not introduce new matter.

IV. Examiner's Grounds for Rejection Based on Publications

The Examiner variously rejected the claims under 35 U.S.C. §§102 or 103 as follows: claims 23-26, 31-33 and 143-145 are rejected under 35 U.S.C. §102(e) as anticipated by Gillies et al., U.S. Patent. Publication 2003/0044423 (hereinafter "Gillies"); claims 23, 25-28, 31-34, 39 and 142-145 are rejected under 35 U.S.C. §102(a) as anticipated by Wu et al., *Protein Engineering* 14:1025-33, 2001 (hereinafter "Wu"); claims 27-28, 34, 40-41, 44, 47 and 102-103 are rejected under 35 U.S.C. §103(a) as obvious over Gillies in view of Shan et al., *J Immunol* 162:6589-95, 1999 (hereinafter "Shan") and Liu et al., *J. Immunol* 139:3521-26, 1987 (hereinafter "Liu"); claims 30, 35-36 and 38 are rejected under 35 U.S.C. §103(a) as obvious over Gillies in view of Kucherlapati et al., U.S. Patent 6,150,584 (hereinafter "Kucherlapati"), and Gilliland et al., *Tissue Antigens* 47:1-20, 1996 (hereinafter "Gilliland"); and claims 48 and 104-106 are rejected under 35 U.S.C. §103(a) as obvious over Gillies in view of Fell et al., *J Biol. Chem* 267:15552-58, 1992 (hereinafter "Fell"), and Gilliland.

V. The Rejection of Claims 23-26, 31-33 and 143-145 under 35 U.S.C. §102(e) as Anticipated by Gillies Should Be Withdrawn

The Examiner rejects claims 23-26, 31-33 and 143-145 under 35 U.S.C. §102(e) as anticipated by Gillies. The Examiner asserts that Gillies describes a hinge region having only two cysteines thereby anticipating independent claim 23 and claims dependent therefrom. The Examiner also alleges that Gillies anticipates independent claim 24, citing a paragraph in Gillies which he asserts means that a molecule with an IgG-derived CH2 region inherently exhibits ADCC and CDC activity (Gillies, paragraph 131). Applicants submit that neither the Gillies priority document nor the Gillies published application describes the single chain proteins recited in the claims as amended.

Claim 23 as amended is directed to a single chain protein having a binding domain, a hinge region containing two cysteines (wherein the hinge region contains two cysteines but the first cysteine found in the wild-type binge is not deleted or substituted in the hinge), an Ig CH2 region polypeptide, and an Ig CH3 region polypeptide, where the single chain protein promotes ADCC and/or CDC function.

The Gillies application describes hinge regions in which the first cysteine is changed to another amino acid and the second and third cysteines are retained (Gillies,

paragraph 101). Gillies does not contemplate a hinge region in which the first cysteine in the region is preserved, as in the present claims. Thus, the hinge regions in Gillies differ from the hinge region recited in claim 23, and as such, Gllies does not disclose each and every element of claim 23.

Claim 24 as amended is directed to a single chain protein having a binding domain, an hinge region containing only one cysteine in the hinge region, a CH2 polypeptide region and an IgG CH3 polypeptide region. The Examiner cites Gillies (paragraph 101), which states that "mutation of one or more cysteines involved in heavy chain homodimerization" can lead to improvement in expression or assembly of the Ig fusion, as anticipatory of claim 24 before amendment. The Examiner further directs Applicants attention to Gillies paragraph 131, asserting that the last sentence of this paragraph indicates that adding an IgG CH2 polypeptide region to any Ig construct necessarily confers effector function.

Gillies Paragraph 131 refers to a construct having a different structure than the presently claimed constructs. This paragraph refers to an Ig fusion construct having multiple valency. See the first sentence of the paragraph. Paragraph 130 defines the constructs in paragraph 131 as proteins that have the CH2 domain of an IgG and the CH3 and CH4 domains of an IgM or IgA. In contrast, amended claim 24 requires a single chain protein having an IgG CH3 region. As such, Gillies does not disclose each and every element recited in amended claim 24.

Because Gillies does not disclose each and every element of either claim 23 or claim 24, the rejection of those claims and dependent claims 25,26, 31-33 and 143-145 under 35 U.S.C. §102(e) over Gillies should be withdrawn.

VI. The Rejection of Claims 23, 25-28, 31-34, 39 and 142 under 35 U.S.C. §102(a) as Anticipated by Wu Should Be Withdrawn

The Examiner rejects claims 23, 25-28, 31-34, 39 and 142-145 under 35 U.S.C. §102(a) as anticipated by Wu. Wu discloses a CD20-specific single chain antibody having a hinge and CH2 and CH3 regions derived from IgG1, wherein the first hinge cysteine is mutated to serine (Wu page 1026, col, 2), but the second and third cysteines are retained.

Claim 23 is directed to a single chain polypeptide having a hinge derived from an IgG or IgA hinge wherein the hinge contains only two cysteine residues, and the first cysteine residue in the hinge region is specifically not substituted. Wu discloses the first cysteine in the hinge region is mutated. As such, Wu does not disclose each and every element of claim 23. The remaining rejected claims ultimately depend from claim 23, and therefore, Wu also does not anticipate any of claims 25-28, 31-34, 39 and 142-145.

The rejection of the claims under 35 U.S.C. §102(a) as anticipated by Wu should be withdrawn.

VII. The Rejection of Claims 27-28, 34, 40-41, 44, 47, and 102-103 under 35 U.S.C. §103(a) Should Be Withdrawn

The Examiner rejects claims 27-28, 34, 40-41, 44, 47, and 102-103 under 35 U.S.C. §103(a) as obvious over Gillies in view of Shan and Liu. The rejected claims are directed to single chain proteins wherein the binding domain is specific for a B cell target biological molecule (claim 27), specifically CD20 (claim 28), and wherein the binding domain is derived from the 2H7 antibody (claims 40-41, 44, 47 and 102-103).

As established in Section VI above, Gillies neither discloses nor suggests a single chain protein as recited in amended claim 23 or 24. Shan describes a CD20-specific single chain antibody having a heavy chain hinge, and both CH2 and CH3 constant regions, wherein the hinge region contains no cysteine residues. Liu teaches the sequence of the 2H7 heavy and light chain variable regions. The chimeric antibody of Liu contains wild-type human IgG1 regions and Liu does not disclose or suggest making a single chain protein using these sequences. Liu also does not disclose or suggest mutating the IgG1 hinge region.

A person of ordinary skill in the art reading Gillies in view of Shan and Liu would not have been led to the single chain proteins recited in either claims 23 or 24 because none of the three references, considered alone or in any combination, discloses or suggests the constructs recited in either claim 23 or 24. Neither Gillies nor Shan nor Liu disclose a hinge region having two cysteines wherein the first cysteine in the hinge is preserved, and neither Gillies nor Shan nor Lui disclose or suggest a construct having one cysteine in the hinge region and further comprising an IgG CH3 region. Nor do the three cited references, alone or in combination, predict that the claimed single chain proteins would retain ADCC

and/or CDC function. As such, one of ordinary skill in the art had no motivation to combine the references, nor would there have a been a reasonable expectation of success based on the cited references, to make a single chain protein of the present invention possessing the requisite effector functions.

Claims 27-28, 34, 40-41, 44, 47 and 102-103, each ultimately depend on claim 23 and/or claim 24. Therefore, the subject matter of any of claims 27-28, 34, 40-41, 44, 47 and 102-103 is not obvious under 35 U.S.C. §103(a) over Gillies in view of Shan and Liu. Accordingly, the rejection should be withdrawn.

VIII. The Rejection of Claims 30, 35-36 and 38 under 35 U.S.C. §103(a) Should Be Withdrawn

The Examiner rejects claims 30, 35-36 and 38 under 35 U.S.C. §103(a) as obvious over Gillies in view of Kucherlapati and Gilliland.

The rejected claims are directed to a single chain protein specific for a B cell target (claim 30) or for various B cell targets and interleukins (claims 35-36), and to single chain proteins specific for various targets involved in cancer and other diseases or conditions (claim 38).

Gillies is discussed above. Kucherlapati describes human single-chain antibodies derived from transgenic mice which may be specific for a variety of cell surface markers, including B cell markers, interleukins and agents involved in cancerous conditions. Gilliland teaches methods for making scFv-Ig constructs for therapeutic applications.

As established in Section VI above, Gillies neither discloses nor suggests a single chain protein according to the present claims. Kucherlapati and Gilliland were cited as teaching that antibodies to many different antigens can be made in single-chain form, but (like Gillies) neither reference discloses or suggests making single chain proteins having the hinge, CH2 and CH3 structure recited in the present claims. A person of ordinary skill in the art reading Gillies in view of Kucherlapati and Gilliland would not have been led to the single chain proteins recited in either claim 23 or 24 because none of the three references, alone or in combination, disclose or suggest a single chain protein possessing a hinge, CH2 and CH3

region as claimed. Nor do the three cited documents, considered alone or in combination, predict that such single chain proteins would retain ADCC and/or CDC function.

Thus, the Examiner has failed to establish a *prima facie* case of obviousness for any of the rejected claims and the rejection of claims 30, 35-36 and 38 under 35 U.S.C. §103(a) as obvious over Gillies in view of Kucherlapati and Gilliland should be withdrawn.

IX. The Rejection of Claims 48 and 104-106 under 35 U.S.C. §103(a) Should be Withdrawn

The Examiner rejects claims 48 and 104-106 under 35 U.S.C. §103(a) as obvious over Gillies in view of Fell and Gilliland. The rejected claims are directed to a single chain polypeptide specific for the L6 antigen.

Gillies and Gilliland have been discussed in Sections VI and IX, respectively. Fell teaches generation of a chimeric L6-specific antibody. The chimeric antibody comprises the mouse L6 variable regions and human IgG1 heavy chain constant regions. Fell neither discloses nor suggests generation of a single chain antibody specific for the L6 antigen, nor does Fell suggest a protein construct as recited in the claims.

The combined disclosures of the three cited documents do not teach or suggest the single chain proteins of the present claims. A person of ordinary skill in the art reading Gillies in view of Fell and Gilliland would not have been led to the single chain proteins recited in claim 23 or 24 because none of the three documents, taken alone or in combination, discloses or suggests the hinge, CH2 and CH3 regions structure recited in the rejected claims. Nor do the three references, considered alone or in combination, predict that such single chain proteins would retain ADCC and/or CDC function.

For the foregoing reasons, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness for any of the rejected claims, and the rejection of claims 48 and 104-106 under 35 U.S.C. §103(a) as obvious over Gillies in view of Fell and Gilliland should be withdrawn.

X. The Rejection of Claims 23, 25-44, 47-48, 102-106 and 142-145 under 35 U.S.C. §112, Second Paragraph, Should be Withdrawn

The Examiner objects to claims 39-44, 47-48 and 142 as allegedly indefinite in the recitation of the phrase "wherein said binding domain polypeptide is a single chain Fv capable of binding CD20." The Examiner asserts that the term "scFv" is unclear in this context.

Applicants submit that the term "scFv" is used in the claim in the same manner in which the Examiner refers to it in the art, as "comprising the heavy and light chain variable regions joined by a short peptide linker." The presence of the first hinge cysteine residue does not alter the structure of the scFv. The hinge cysteine does not transform the scFv into a Fab, does not require/acquire a light chain constant region, and the protein remains functional. In other words, the term "scFv" should be given its ordinary meaning because the presence of the first cysteine in the hinge region is a structural attribute that the single chain protein possesses that does not alter the intended and art-recognized function of an scFv.

The Examiner rejects claims 23, 25-44, 47-48 102-105 and 142-145 as allegedly indefinite in the recitation of the phrase "wherein said hinge peptide is an IgG or an IgA hinge peptide in which the number of cysteine residues is reduced to two, provided that when the hinge peptide contains two cysteines the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally occurring IgG or IgA antibody is not deleted or substituted."

Applicants have amended claim 23 to remove the language the Examiner interpreted as conditional.

The rejection of the claims as indefinite should therefore be withdrawn.

XI. Conclusion

Applicants respectfully submit that the claims are in condition for allowance and request early notification of same.

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Respectfully submitted,

By _____

Katherine L. Neville
Registration No.: 53,379
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Agent for Applicants